REMARKS

Claims 1, 4, 6-7, 9-11, and 17-27 are pending. Claims 2, 3, 5, 8 and 12-16 were cancelled. Claims 6 and 18-20 are withdrawn. Claims 1, 4, 7, 9-11, 17 and 21-27 stand rejected. Applicants have amended claims 1 and 17, and canceled claims 4, 11 and 25 without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of those claims in this or another patent application. Applicants request entry of the amendment and reconsideration of the outstanding rejections.

Amendments to the Claims

Applicants have amended claim 1 by importing into it the elements of claim 4, thereby replacing the phrase "a solid tumor" with "renal cell carcinoma (RCC)." Applicants submit that no new matter is introduced by this amendment, since support for the amendment can be found, for example, at paragraphs [0006] and [0017], and originally-filed claim 4. Claim 1 has also been amended to define "reference expression profile" as "a baseline-expression profile of said at least one CCI-779 activity gene in a peripheral blood sample isolated from one or more patients before CCI-779 treatment." Support for this amendment can be found, for example, at paragraph [0009].

Applicants have amended claim 17 by replacing "a solid tumor" with "renal cell carcinoma (RCC)," and by defining the reference peripheral blood sample as being "isolated from one or more patients before CCI-779 treatment." Support for these amendments can be found, for example, at paragraphs [0006], [0017], and [0009], respectively. No new matter is introduced by these amendments.

Applicants request the entry of the amendments under 37 C.F.R. § 1.116(b) because the amendments to the claims either cancel claims, comply with requirements of form expressly set forth in a previous Office Action, or present the rejected claims in better form for consideration on appeal.

Oath and Declaration

Applicants submit herewith corrected declarations, which identify the citizenship of each inventor. Applicants wish to thank the Examiner for holding this objection against

the defective declaration in abeyance to provide the Applicants the opportunity to collect the inventors' signatures.

Previous Rejections

Applicants wish to thank the Examiner for withdrawing the rejection to (a) claims 1, 4, 7, 9 and 10 under §112 (second paragraph) and (b) claims 1, 9-11 and 17 under §102(b).

Rejections under 35 USC § 112 1st ¶, enablement

Claims 1, 4, 7, 9-11, 17 and 21-27 stand rejected for allegedly failing to enable one skilled in the art to make and/or use the invention. The rejection is based upon the Wands factors and is summarized below. Applicants' responses to the rejections are provided therewith.

1. Nature of the Invention and Breadth of Claims

The Office alleges that the invention is broad in scope and very complex because it comprises: "the use of any gene or set of genes from selected from among the 310 genes of table 5", sourcing PBMCs from "any patient having any solid tumor", and comparing the expression profile to "any reference peripheral blood sample from said patient," (Office action of 10/29/2007, page 7).

Applicants respectfully assert that the claims as amended are not overly broad in view of the disclosure and the ordinary knowledge in the art. Independent claim 1 is currently directed to a method of detecting in vivo CCI-779 activity in a patient having renal cell carcinoma (RCC), including the steps of generating an expression profile of any one or more of Table 5 markers in a peripheral blood sample of the RCC patient and comparing that profile to a baseline reference profile from one or more patients prior to receiving CCI-779 treatment, such that a significant difference between the reference profile and expression profile indicates in vivo CCI-779 activity. As such, the claim is hence directed to those patients suffering from RCC, which is described for example at paragraphs [0036] – [0039] and exemplified at Example 2 (paragraph [0464]). The reference expression profile is limited to a base-line expression profile determined from samples obtained from RCC patients prior to CCI-779 treatment, which is exemplified,

for example, at Example 3, paragraph [0469]. Furthermore, the markers to which the claim are directed are those markers which are significantly differentially expressed in PBMCs from RCC patients treated with CCI-779. Those markers are explicitly defined in Tables 2 – 5, and their structures are clearly depicted in the sequence listing as SEQ ID NOs: 1 – 310. While Table 5 does depict a list of more than one marker, such a list is fully enabled by the instant specification. The skilled artisan would readily recognize that the change in gene expression of any one or more of those markers upon administering CCI-779 to a RCC patient, relative to the base-line reference, indicates an *in vivo* effect of CCI-779.

2. Guidance Provided by the Specification and the Existence of Working Examples

The Office alleges that Applicants present no guidance and no working examples "with regards to reference samples taken after a CCI-779 exposure," and contends that "the specification does not provide a single working example ... indicative of the in vivo activity of the drug therapy ... upon the solid tumor," (Office action of 10/29/2007, page 8).

Applicants respectfully note that the claims as amended provide a reference expression profile that is established from PBMCs taken from patients prior to CCI-779 administration, which is exemplified, for example, in working Example 3.

Furthermore, Applicants traverse the assertion by the Office that the claims require a nexus between in vivo CCI-779 activity as a change in marker expression in PBMCs, and an effect of CCI-779 on RCC, whereby a change in PBMC markers mirrors an effect on RCC tumors. The claims as presented do not provide that such a nexus be made. The claims merely recite an in vivo effect on PBMC marker gene expression.

3. State of the Prior Art and Level of Predictability in the Art

The Office contends that "the skilled artisan would [not] be able to extrapolate from the disclosed CCI-779-modulated genes and the knowledge available in the art regarding the correlated effects of drug therapy upon any solid tumor and the simultaneous changes in PBMC gene expression, such that the skilled artisan could practice the claimed method to determine if changes in the PBMC expression profiles before and and/or at different stages of drug treatment were indicative of the in vivo activity of the drug on the solid tumor," (Office action of 10/29/2007, page 9 last paragraph to first paragraph of page 10.) The Office also contends that "the utility of a

putative endpoint for any disease state is unpredictable and must be validated," (Office action of 10/29/2007, page 11.)

Applicants respectfully traverse the Office's assertion that the *in vivo* effects of CCI-779, as provided in the claims, must include experimental correlation between an observed effect in marker expression in PBMCs (which is supported in the instant specification with working examples) and an effect in a tumor/RCC. The present claims do not require *per se* that PBMCs act as surrogates in the determination of efficacy of CCI-779 treatment in patients with RCC. Thus, Applicants respectfully submit that the requirement that the specification must enable the determination of the effectiveness of CCI-779 therapy toward RCC or any other solid tumor is not proper in view of the pending claims.

4. Amount of Experimentation Necessary

The Office alleges that an undue amount of experimentation is required to "accurately determine gene expression differences in PBMCs of patients with a solid tumor before and/or after different stages of drug treatment;" and then "to determine which of those differences were indeed indicative of the drug therapy ... activity in vivo." The Office also reiterates its position that the "in vivo drug activity on PBMC gene expression and upon the solid tumor would need to be correlated," (Office action of 10/29/2007, page 12.)

Applicants submit that the pending claims provide for assessing an expression profile in PBMCs after CCI-779 treatment, compared to a base-line reference expression profile obtained prior to CCI-779 treatment. The gene expression markers, which were empirically determined to change in response to CCI-779 administered to patients, are presented, for example, in Tables 2 – 5. Each of the markers were empirically determined to change significantly in response to CCI-779 treatment, thereby actually showing an *in vivo* effect due to CCI-779. Applicants again traverse the assertion of the Office that a nexus be established between the *in vivo* effects as expressed in PBMCs and an effect upon the solid tumor. The effect of CCI-779 upon the PBMCs *in vivo*, either directly or indirectly, in terms of differential marker expression, has been established in the working examples and in the resultant tables 2 – 5.

In light of the arguments presented herein, Applicants assert that the currently presented claims are enabled. Accordingly, Applicants request withdrawal of the rejection of claims 1, 7, 9, 10, 17 and 21-27 under 35 U.S.C. § 112, 1ST paragraph (enablement).

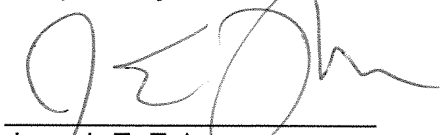
Double Patenting

Claims 1, 4 and 10 - 11 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1 - 3 of co-pending application, U.S. Serial No. 10/793,032. Applicants request that the provisional nonstatutory obviousness-type double patenting rejection be held in abeyance until such time that the presence of otherwise-allowable subject matter is acknowledged. At such time, Applicants are prepared to file an appropriate terminal disclaimer over the co-pending application, U.S. Serial No. 10/793,032.

CONCLUSION

In view of the foregoing, Applicants believe that all rejections have been overcome and claims 1, 7, 9, 10, 17 and 21-27 are now in a condition for allowance. The Examiner is invited to call the undersigned agent to discuss any remaining issues.

Respectfully submitted,



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